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Prognostic association of depression following myocardial infarction with mortality and cardiovascular events: a meta-analysis of 25 years of research

Anna Meijer, M.Sc.[a,*], Henk Jan Conradi, Ph.D.[a,b], Elisabeth H. Bos, Ph.D.[a,c], Brett D. Thombs, Ph.D.[d,e], Joost P. van Melle, M.D., Ph.D.[f], Peter de Jonge, Ph.D.[a,g]

[a]*Interdisciplinary Center for Psychiatric Epidemiology, University Medical Center Groningen/University of Groningen, The Netherlands*
[b]*Department of Clinical Psychology, University of Amsterdam, The Netherlands*
[c]*Center for Integrative Psychiatry, Lentis, Groningen, The Netherlands*
[d]*Departments of Psychiatry; Epidemiology, Biostatistics, and Occupational Health; and Medicine, McGill University, Montréal, Quebec, Canada*
[e]*Department of Psychiatry, Center for Clinical Epidemiology and Community Studies, and Department of Medicine, Jewish General Hospital, Montréal, Quebec, Canada*
[f]*Department of Cardiology, University Medical Center Groningen, The Netherlands*
[g]*Center of Research on Psychology and Somatic Disease, Department of Medical Psychology, Tilburg University, The Netherlands*

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Abstract

Objective: A meta-analysis of over 25 years of research into the relationship between post-myocardial infarction (MI) depression and cardiac prognosis was conducted to investigate changes in this association over time and to investigate subgroup effects.
Method: A systematic literature search was performed (Medline, Embase and PsycINFO; 1975–2011) without language restrictions. Studies investigating the impact of post-MI depression on cardiovascular outcome, defined as all-cause mortality, cardiac mortality and cardiac events within 24 months after the index MI, were identified. Depression had to be assessed within 3 months after MI using established instruments. Pooled odds ratios (ORs) were calculated using a random effects model.
Results: A total of 29 studies were identified, resulting in 41 comparisons. Follow-up (on average 16 months) was described for 16,889 MI patients. Post-MI depression was associated with an increased risk of all-cause mortality [(OR), 2.25; 95% confidence interval [CI], 1.73–2.93; $P<.001$], cardiac mortality (OR, 2.71; 95% CI, 1.68–4.36; $P<.001$) and cardiac events (OR, 1.59; 95% CI, 1.37–1.85; $P<.001$). ORs proved robust in subgroup analyses but declined over the years for cardiac events.
Conclusions: Post-MI depression is associated with a 1.6- to 2.7-fold increased risk of impaired outcomes within 24 months. This association has been relatively stable over the past 25 years.

Keywords: Depression; Myocardial infarction; Prognosis; Mortality; Meta-analysis

1. Introduction

Beginning in the 1980s, reports that psychosocial stress and depression following myocardial infarction (MI) were linked to prognosis accumulated [1–5]. The increasing number of studies showing links between post-MI depression and prognosis suggested that identifying and treating depression in MI patients could contribute to improving survival rates and overall prognosis.

In the 25 years since these first investigations, much research has been done in this field, which has been summarized in several meta-analyses [6–8]. This research showed that depressed cardiac patients have an increased risk of both fatal and nonfatal events (including patients with depressive disorder and patients with elevated symptoms of

* Corresponding author. Tel.: +31 50 3613833.
E-mail address: anna.meijer@med.umcg.nl (A. Meijer).

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depression based on self-report questionnaires) compared with those without depression. Barth et al. [6] performed a meta-analysis on 29 studies concerning patients with coronary heart disease (CHD), most of which were MI patients. They found that depression in MI patients was associated with a 2.0 to 2.6 times higher risk of mortality. Similarly, in a meta-analysis of 22 studies, Van Melle et al. [8] found an increased risk of 2.0 to 2.5 of poor cardiac or mortality outcomes within 2 years after an MI in patients with depression compared with nondepressed patients. The most recent meta-analysis by Nicholson et al. [7] reviewed studies published up to 2004 and reported that depressed post-MI patients had a 2.1 times higher risk of mortality than nondepressed patients. Hence, in summary, previous meta-analyses demonstrated that depressed post-MI patients have a 2.0 to 2.6 times increased risk of adverse outcomes compared with nondepressed post-MI patients.

A fair number of important studies on post-MI depression and (cardiac) prognosis have been published in the 7 years since previous literature searches. In addition, none of the existing meta-analyses have statistically investigated whether the association of depression with mortality or cardiac events changes over time, as has been suggested earlier [8,9]. This is an important question, as new insights in study design and statistical methodology as well as advances in the treatment and prevention of MI in recent years can affect the nature and strength of the association between post-MI depression and prognosis.

Therefore, the main objective of this study was to perform a new meta-analysis to summarize the association between post-MI depression and prognosis, defined as all-cause mortality, cardiac mortality and cardiac events that occurred within 24 months after the index MI. A secondary goal was to investigate whether the strength of the relationship between depression and cardiac outcomes has changed over the years and whether or not methodological factors influence this relationship.

2. Methods

2.1. Literature search

A literature search was performed on January 5, 2011, to identify prognostic studies that investigated the association between post-MI depression and (cardiovascular) prognosis published since our previous literature search in January 2004 [8]. The combined search results included literature published since 1975. Relevant articles were selected from the electronic databases Medline (PubMed), Embase and PsycINFO without language restrictions. For this purpose, search terms related to depression and MI were used and customized to the search strategies of each database. Full-search strings for each database are listed in Appendix 1. In addition to the database searches, major reviews and relevant articles were cross-referenced. When necessary, additional information was requested from authors by e-mail.

2.2. Study selection

2.2.1. Inclusion and exclusion criteria

Studies that met the following criteria were eligible for inclusion: patients were hospitalized for MI; a validated depression rating scale or structured diagnostic interview was used; depression was measured within 3 months after the MI; studies were prospective, reporting on (cardiovascular) prognosis in depressed versus nondepressed patients; study outcome was all-cause mortality, cardiac mortality or cardiac events; and the end point was within 24 months after the index MI. For the end-point cardiac events, studies that reported on cardiac death, cardiac arrest, recurrent MI, cardiac rehospitalization or a combination of the above were included. Depression was defined as either depressive disorder or elevated symptoms of depression.

Selection of studies identified by the literature search was done by three independent raters (J.v.M., P.d.J. and A.M.) in two phases. First, a title abstract review was performed, in which studies that clearly did not meet the inclusion criteria were excluded. Second, full texts were retrieved and reviewed for the articles that were selected as potentially eligible for inclusion in the title–abstract review. In the review process, reviews, meta-analyses, comments, letters, editorials, case reports and design reports of studies as well as studies that did not include depression as a mood state (but, for example, ST-segment depression) were excluded.

Only studies on data of MI patients were included to create a relatively homogeneous group of subjects. Furthermore, the end point was chosen to be within 2 years after MI, as we were interested in relatively short-term effects of post-MI depression on prognosis. Most mortality and new events after MI occur within the first few months, so it was expected that any association with post-MI depression would be evident by 2 years. By using a 2-year follow-up period, relevant studies with varying follow-up durations could best be compared. If studies reported outcomes later than 2 years after the index MI, authors were contacted to request data on 2-year outcomes.

When multiple articles were based on the same dataset, those with the best methodological quality or those that were most informative were selected (i.e., more subjects, longer follow-up, etc.). However, when multiple articles were based on the same subjects, but reported on different, not overlapping outcomes, they were all included.

When studies included MI patients as a subgroup of acute coronary syndrome, and it was recorded whether patients had unstable angina or MI, the authors were asked for depression and outcome data for MI patients only.

2.3. Quality assessment

Reporting the quality of studies included in meta-analyses is recommended by experts [10], as the quality of

the results of a meta-analysis largely depends on the quality of included studies. In addition, quality assessment may be helpful in deciding which variables measured in the studies of the meta-analysis could be used in subgroup or sensitivity analyses. Therefore, included articles were assessed according to the following six methodological quality criteria: (1) sample size of each group (preferably at least 25 patients per group); (2) representativeness of the population (i.e., whether the sample had any specific inclusion or exclusion criteria such as those based on age or gender); (3) whether there was more than 25% loss to follow-up; (4) whether studies controlled for at least three of the following: hypertension, smoking, hypercholesterolemia, diabetes mellitus, left ventricular ejection fraction (LVEF) or previous MI; (5) whether clinical end points were scored adequately, that is, by means of central death registry, chart review or independent blinded end point committee and (6) whether depression was measured using a structured diagnostic interview or a self-report instrument.

2.4. Data analysis

Data analyses for the summary estimate of the odds ratios (ORs) were performed separately for three outcomes: all-cause mortality, cardiac mortality and cardiac events. First, data from the included studies were pooled. Reported results were converted into raw data (2×2 tables) and dichotomized outcomes. Then, pooled ORs and 95% confidence intervals (CIs) were calculated using MIX 1.7, a statistical package designed for performing meta-analyses [11], using a random effects model [12]. When studies reported both clinically diagnosed major depressive disorder and depressive symptoms, data on major depressive disorder were included. To test between-study variance, heterogeneity tests were

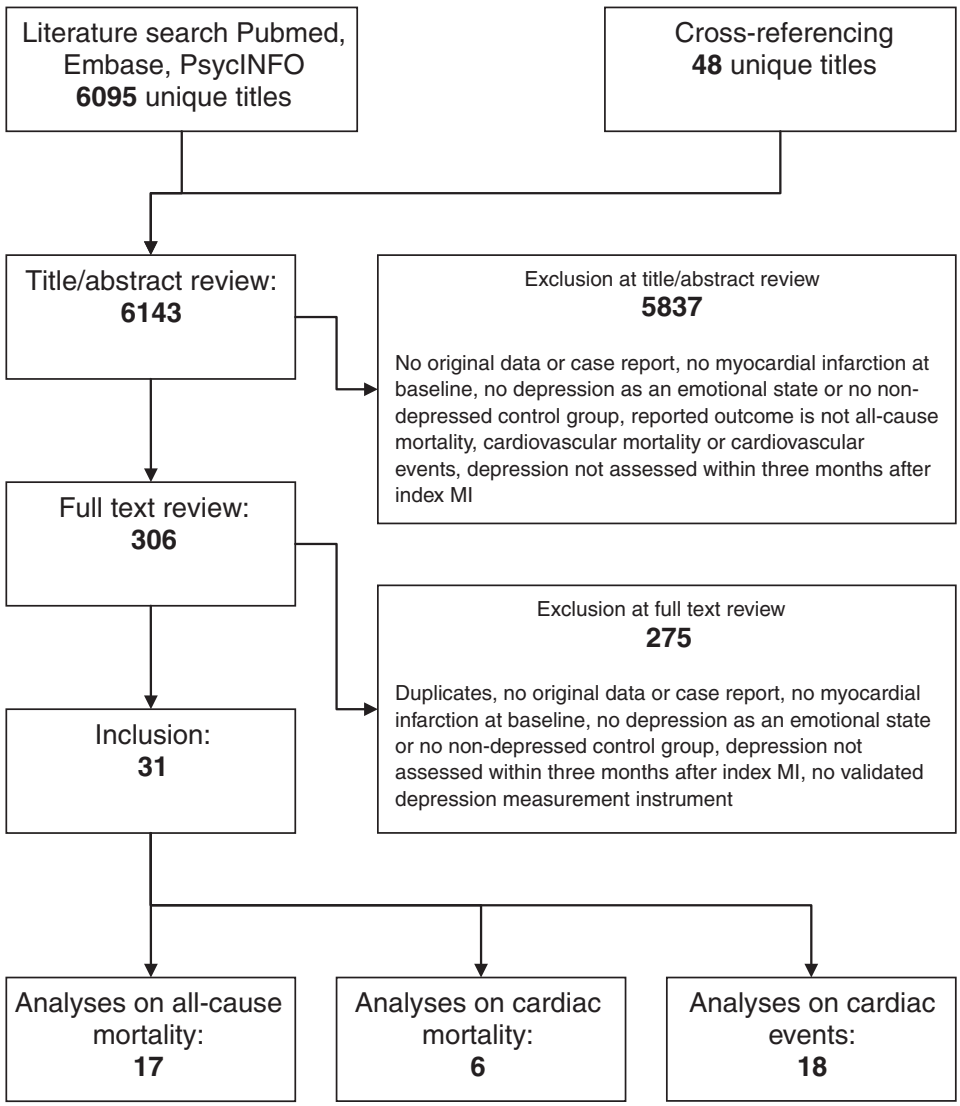

Fig. 1. Flowchart literature search.

Table 1
Overview and summary of included studies

First author	Year of publication	N	Mean age (years)	% Female	Instrument	Cutoff	Time post-MI (days)	% Depression	Outcome	FU time (months)	% Lost to FU	Start data collection
Ahern et al. [1]	1990	351	NA	NA	BDI	NA	6–60	40	CE	12	1	1983
Carney et al. [13]	2009	1328	60	45	DISH/BDI	BDI cutoff NA	<28	69	ACM	24	NA	1996
De Jonge et al. [14]	2006	468	61	20	CIDI	NA	90	25	CE	24	NA	1997
Denollet et al. [15]	2010	416	60	22	BDI	NA	61	24	CE	24	0	2003
Doyle et al. [16]	2006	433	63	25	HADS-D/BDI-FS	HADS-D >7; BDI-FS >3	2–5	17	ACM	12	0	2003
Doyle et al. [17]	2010	285	61	20	HADS-D/BDI-FS	HADS-D >7; BDI-FS >3	2–4	27	CE	15	0	2006
Drago et al. [18]	2007	98	62	22	BDI/DSM-IV structured interview	BDI ≥10	7-14	BDI: 34; SCID: 14	ACM/CE	24	2	1999
Frasure-Smith et al. [19]	1999	896	59	32	BDI	BDI ≥10	5–15	32	CM	12	0	1991
Frasure-Smith et al. [20]	1995	218	60	22	BDI/DIS	BDI ≥10	5–15	BDI: 31; DIS: 16	CE	12	0	1991
Irvine et al. [21]	1999	301	64	18	BDI	BDI ≥10	6–45	33	ACM/CM	24	5	1990
Kaufmann et al. [22]	1999	331	65	34	DIS	DIS ≥5	7	27	ACM	12	0	1995
Ladwig et al. [2]	1991	553	54	0	KSb-S	90%	17–21	14	CM/CE	6	0	1983
Lane et al. [23]	2000	284	63	25	BDI	BDI ≥10	2–15	31	CM	12	1	1997
Lane et al. [24]	2001	272	63	25	BDI	BDI ≥10	2–15	31	CE	12	6	1997
Lauzon et al. [25]	2003	550	60	21	BDI	BDI ≥10	2–3	35	ACM/CE	12	0	1996
Lesperance et al. [26]	1996	222	60	22	BDI/DIS	BDI ≥10	5–15	16	ACM	18	0	1991
Mayou et al. [27]	2000	344	63	27	HADS	HADS >10	<3	8	ACM	18	0	1994
Nakatani et al. [28]	2005	1803	NA	NA	Zung SDS	Zung SDS≥40	<90	48	CE	24	0	1999
Parakh et al. [29]	2008	284	64	43	BDI/SCID	BDI ≥10	<5	27	ACM	24	0	1995
Parashar et al. [30]	2006	1881	61	32	PHQ	PHQ ≥10	<31	27	ACM	6	NA	2003
Rafanelli et al. [31]	2003	61	61	17	Modified SCID/DCPR/PSI	NA	30	11	CE	24	0	1995
Rumsfeld et al. [32]	2005	634	65	28	MOS-D	MOS-D ≥0.06	3–14	23	ACM/CE	24	NA	1999
Shiotani et al. [33]	2002	1042	63	20	Zung SDS	Zung SDS ≥40	63	42	CM/CE	12	1	1998
Silverstone [3]	1987	108	63	25	MADRS	MADRS ≥14	1	44	ACM/CE	0.25	NA	1984
Smolderen et al. [34]	2009	2347	61	32	PHQ-9	PHQ ≥10	1–3	22	ACM/CE	24	2	2003
Sørensen et al. [35]	2006	761	59	24	MDI	MDI cutoff NA	±7	10	ACM/CE	12	NA	1999
Steeds et al. [36]	2004	131	60	33	BDI-II	BDI-II ≥12	±7	47	ACM	24	NA	1999
Strik et al. [37]	2003	206	59	24	SCID	NA	30	31	ACM/CE	6	0	1997
Sydeman [38]	1998	101	62	40	SCID/BDI	BDI ≥10	2–7	5	CE	6	7	1996
Thombs et al. [39]	2008	416	61	25	BDI	BDI ≥10	2–5	29	ACM	12	0	1997
Welin et al. [40]	2000	267	NA	16	Zung SDS	Zung SDS ≥40	30	37	CM	24	3	1985

NA, not available; ACM, all-cause mortality; CM, cardiac mortality; CE, cardiac events; BDI, Beck Depression Inventory; BDI-FS, Beck Depression Inventory Fast Scale; CIDI, Composite International Diagnostic Interview; DCPR, Diagnostic Criteria in Psychosomatic Research; DIS, Diagnostic Interview Schedule; DISH, Depression Interview and Structured Hamilton; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders version IV; HADS-D, Hospital Anxiety and Depression Scale–Depression; KSb-S, Klinische Selbstbeurteilungsskalen aus dem Münchner psychiatrische Informations-System; MADRS, Montgomery–Åsberg Depression Rating Scale; MDI, Major Depression Inventory; MOS-D, Medical Outcomes Study–Depression; PHQ, Patient Health Questionnaire; PSI, Psychosocial Index; SCID, Structured Clinical Interview for DSM; Zung SDS, Zung Self-rating Depression Scale.

performed using the Q and I^2 statistics. Possible publication bias was investigated using funnel plots and Egger tests.

Second, to investigate whether the association between post-MI depression and cardiac prognosis changed over time, individual, unadjusted ORs were used and changes over time were investigated using STATA 11 (Statacorp LP, College Station, TX, USA). Different meta-regression models were applied to investigate whether there was any trend in the ORs over time. Null, linear, quadratic and cubic models were applied, and best-fitting models were selected using the Schwarz Bayesian Information Criterion (BIC). The year of the start of data collection (study start) was used as independent variable instead of the year of publication, as there may be a considerable time lag between the period a study is performed and the time it is published. Analyses were weighted for the number of subjects in each study, in such a way that larger studies contributed more to the pooled OR than smaller studies.

Third, subgroup analyses were performed in MIX 1.7 for two methodological differences between studies: type of

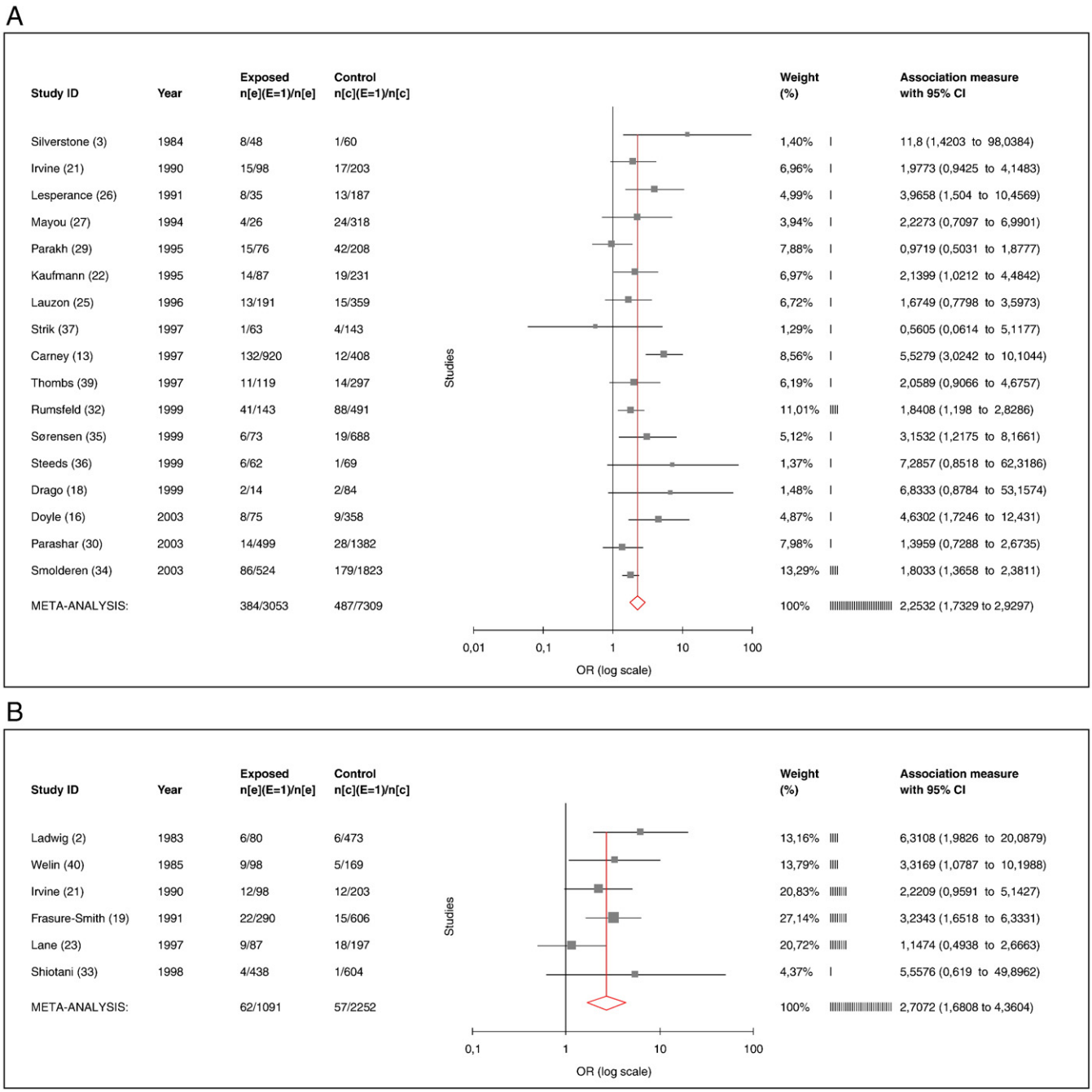

Fig. 2. (A) Forest plot all-cause mortality. (B) Forest plot cardiac mortality. (C) Forest plot cardiac events.

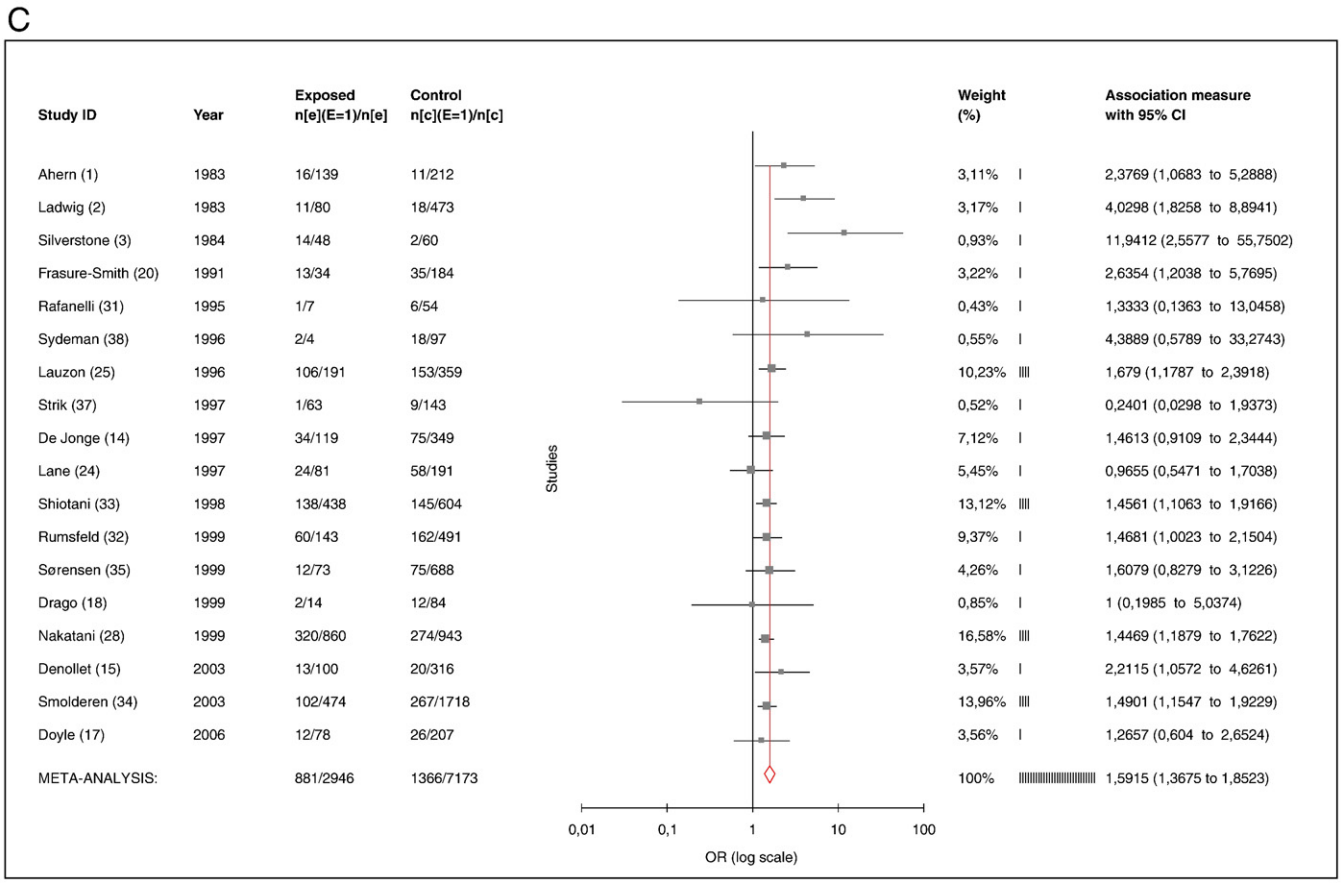

Fig. 2 (*continued*).

depression instrument (structured diagnostic interview vs. self-rating) and number of subjects per study (dichotomized smaller N vs. larger N). For each outcome, studies were divided into subgroups, and separate ORs were calculated. ORs were then compared with a χ^2 test.

3. Results

3.1. Literature search and selection

The literature search resulted in 6,095 unique titles/abstracts. Cross-referencing and personal contacts resulted in an additional 48 potentially eligible articles. After the review and selection process, 31 articles reporting on 29 studies were selected and included, reporting on 16,889 patients (5,353 depressed and 11,536 nondepressed) and representing 41 different analyses. Most of the ineligible articles were excluded because they were not based on original data, such as reviews, case-reports and editorials; because they did not select subjects based on the presence of MI; or because they did not include depression as an emotional state or as a risk factor for poor prognosis. Interrater reliability between the two sets of reviewers (J.v.M.–P.d.J. and P.d.J.–A.M.) was calculated for the full-text review (Cohen's k=0.80 and 0.86, respectively). Fig. 1 is a flowchart of the search results.

Ten authors were contacted to request additional information. Requests were made for outcome data at 24 months post-MI, data for depressed patients only instead of patients with depression or anxiety, duration of follow-up, exact number of events in depressed versus nodepressed groups, data on MI patients only instead of acute coronary syndrome patients, timing of depression measurement after the MI, year in which the study started, loss to follow-up and which depression rating instrument was used. Seven authors provided the requested information. Three authors could not answer, or did not respond to the request, which in these cases meant their studies could not be included in the meta-analysis.

3.2. Main study characteristics

In Table 1, the main study characteristics of included articles are summarized. Collectively, the combined samples included 16,889 patients. Mean patient age at the time of the index MI was 61 years (range, 54–65 years). Twenty-six percent of patients were women, and mean follow-up time was 16 months, ranging from 1 week to 24 months. The proportion of patients with major depression or patients scoring above the cutoff of self-rating instruments ranged from 5 to 69% (average 28%). This proportion was relatively

high in some studies, as they purposefully included more depressed patients. The average percentage of all-cause mortality was 9% (range, 2%–21%); cardiac mortality, 5% (0.5%–10%) and cardiac events, 21% (range, 5%–47%).

3.3. Association between post-MI depression and prognosis

Seventeen studies, consisting of 10,362 patients, reported on all-cause mortality. A total of 892 patients died within 2 years after the index MI. The pooled OR of all-cause mortality after MI in 3,053 depressed patients compared with 7,309 nondepressed patients was 2.25 (95% CI, 1.73–2.93; $P<.001$; Fig. 2A). The studies were statistically heterogeneous [$Q=30.15$, $P=.02$; $I^2=46.93\%$ (95% CI, 6.62–69.84)].

Cardiac mortality was reported in six studies, consisting of 3,343 patients. A total of 119 patients died of cardiac causes within 2 years after the index MI. The pooled OR of cardiac mortality after MI in 1,091 depressed patients compared with 2,252 nondepressed patients was 2.71 (95% CI, 1.68–4.36; $P<.001$; Fig. 2B). The six studies were relatively homogeneous [$Q=7.06$, $P=.22$; $I^2=29.14$ (95% CI, 0.00–70.97)].

Cardiac events (fatal and nonfatal) were reported in 18 studies, consisting of 10,119 patients. A total of 2,247 patients had another cardiac event within 2 years after the index MI. The pooled OR of cardiac mortality after MI in 2,946 depressed patients compared with 7,173 nondepressed patients was 1.59 (95% CI, 1.37–1.85; $P<.001$; Fig. 2C). The 18 studies were statistically homogeneous [$Q=24.5$, $P=.11$; $I^2=30.64$ (95% CI, 0–60.8)].

For the three meta-analyses, funnel plots and Egger tests showed no evidence of publication bias. Table 2 summarizes the three meta-analyses, including the heterogeneity and publication bias tests. Funnel plots are shown in Fig. 3A–C.

3.4. Adjusted associations

Eight studies reported associations adjusted for baseline demographic and cardiac disease severity variables. These adjusted and unadjusted ORs were compared to gain insight into the role of cardiac disease severity and other confounding variables in the association between post-MI depression and prognosis. The studies reporting adjusted associations were too few and heterogeneous to pool by meta-analysis. Therefore, adjusted and unadjusted associations as they were reported in the original articles are simply listed in Table 3. Note that the associations are not necessarily reported as ORs but also as hazard ratios. However, when the frequency of

Table 2
Results meta-analyses, heterogeneity, and publication bias

Outcome	Pooled OR	95 % CI	I^2 (95% CI)	Q (P)	Egger test (P)
All-cause mortality	2.25*	1.73–2.93	46.93 (6.62–69.84)	30.15 (.02)	0.99 (.13)
Cardiac mortality	2.71*	1.68–4.36	29.14 (0–70.97)	7.06 (.22)	1.35 (.46)
Cardiac events	1.59*	1.37–1.85	30.64 (0–60.80)	24.50 (.11)	0.64 (.20)

* $P<.001$.

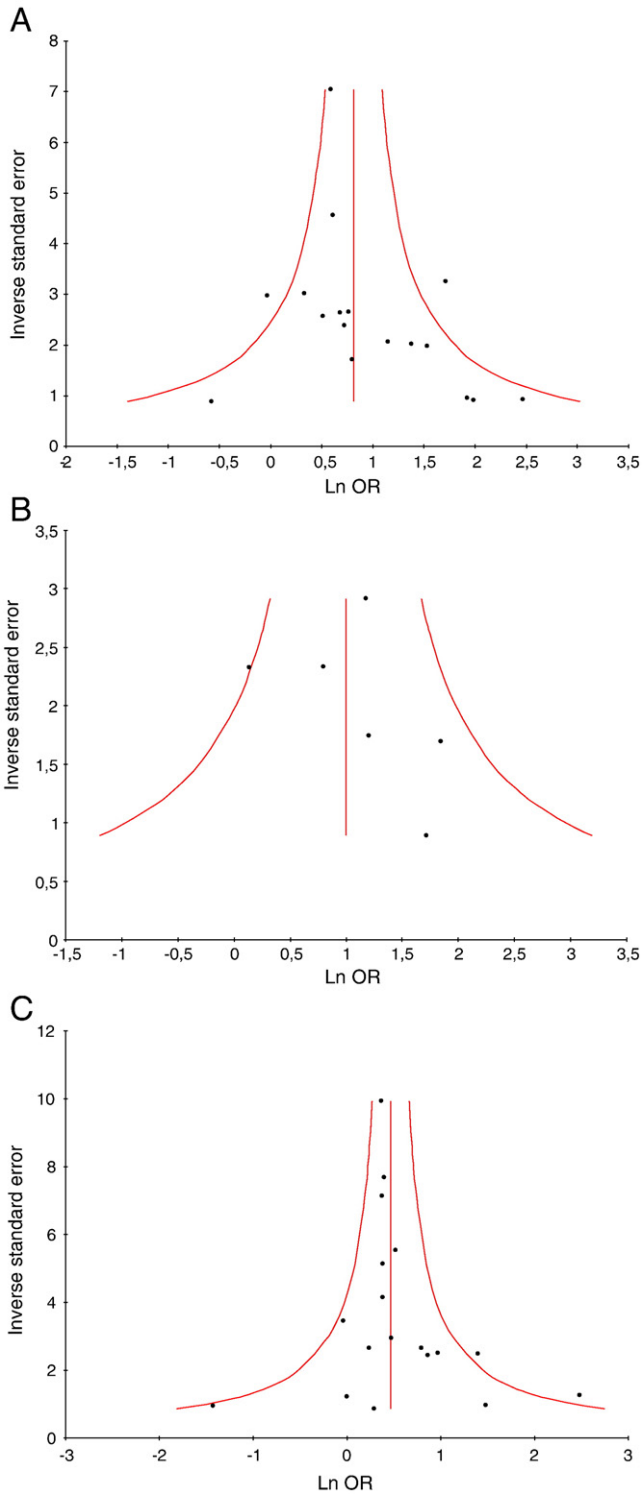

Fig. 3. (A) Funnel plot studies all-cause mortality. (B) Funnel plot studies cardiac mortality. (C) Funnel plot studies cardiac events.

Table 3
Adjusted association per study

Author	Outcome	Unadjusted association (95% CI)	Adjusted association (95% CI)	Variables adjusted for
Frasure-Smith et al. [19]	Cardiac mortality	OR, 3.23 (1.65–6.33)	OR, 3.66 (1.68–7.99)	Age, smoking, LVEF, non-Q-wave MI, Killip class
Frasure-Smith et al. [20]	Cardiac events	OR, 3.32[a] (1.69–6.53)	OR, 1.99[a] (0.92–4.31)	Previous MI, ACE inhibitors at discharge, previous depression, anxiety
Ladwig et al. [2]	Cardiac mortality	OR, 6.31[b] (1.98–20.09)	OR, 4.9[b] (NA)	Recurrent MI, late potentials, dyspnea, occurrence of triples or more complex arrhythmias in 24 h. Holter ECG
Lauzon et al. [25]	Cardiac events	HR, 1.68 (1.18–2.39)	HR, 1.40 (1.05–1.86)	Age, sex, prior MI, history of angina, anterior location of infarct, diabetes mellitus, hypertension, smoking
Rumsfeld et al. [32]	All-cause mortality cardiac events	HR, 1.84 (1.20–2.83) HR, 1.47 (1.00–2.15)	HR, 1.71 (1.11–2.63) HR, 1.41 (1.03–1.93)	Sex, age, race, BMI, blood pressure, LVEF, prior heart failure, prior MI, atrial fibrillation, reperfusion or revascularization during hospitalization for index MI, smoking, hypertension, diabetes, dyslipidemia, COPD, stroke or TIA, renal failure, alcohol use, ACE/ARB, β-blockers, diuretics, aspirin, statins
Shiotani et al. [33]	Cardiac events	OR, 1.46 (1.11–1.92)	OR, 1.41 (1.03–1.92)	Age, gender, severity of MI, diabetes mellitus, hypertension, smoking
Smolderen et al. [34]	Cardiac events	HR, 1.37 (1.16–161)	HR, 1.23 (1.04–1.46)	Age, sex, race, diabetes mellitus, prior CAD, stroke, chronic renal or heart failure, chronic lung disease, nonskin cancer, current smoking, BMI, marital status, education, insurance status, working status, ST-elevation AMI, LVEF, heart rate, angiography, revascularization, percentage/number of quality of care indicators received
Sørensen et al. [35]	All-cause mortality	HR, 3.15 (1.22–8.17)	HR, 1.10 (0.10–9.00)	Age, single status, non-Q-wave infarction, LVEF, workload (watts)

ACE, angiotensin-converting enzyme; ARB, Angiotensin Receptor Blocking Agents; BMI, body mass index; CAD, Coronary Artery Disease; COPD, chronic obstructive pulmonary disease; TIA, transient ischemic attack; AMI, acute myocardial infarction.

[a] These numbers represent BDI depressive symptoms, while for the meta-analysis, Diagnostic Interview Schedule major depression was used.

[b] The authors distinguished between low, medium and high depression. The unadjusted OR is for high versus medium or low depression. The adjusted OR is for low versus high depression.

events among subjects is low, which is the case with mortality or cardiac events, these numbers are roughly comparable [41,42]. In seven of the eight studies, adjusted associations were smaller than unadjusted associations. The attenuation ranged from 4% to 65% and was, on average, 21%.

3.5. Secondary analyses

3.5.1. Changes in ORs over time

There was no association between the year of study start and the OR for the outcome all-cause mortality. Fig. 4A shows the ORs against time. For the outcome cardiac mortality, the number of studies (6) was too small to perform a meta-regression.

There was a significant linear association between the year of study start and the OR for the outcome cardiac events [linear model $F(1.13)$, $P=.01$, $R^2=0.29$, BIC=58.12]. This means that later studies generally reported lower ORs than earlier studies. The linear model, however, was only slightly better than the quadratic model [quadratic model $F(2,43)$, $P=.02$, $R^2=0.40$, BIC=59.17]. When the analysis was rerun without an outlier, again to assess the robustness of the association, there was a superior model fit for the quadratic association [quadratic model ($F(2,42)$, $R^2=0.55$, $P<.01$, BIC=31.49) vs. linear model ($F(1,43)$, $R^2=0.46$, $P<.01$, BIC=32.37)]. This means that the decline was somewhat stronger in the earlier years and weakened in the later years. Overall, there was a decline in the OR of about 0.1 each year (Fig. 4B).

3.6. Differences between structured diagnostic interviews and self-rating instruments

For the outcome all-cause mortality, 6 studies (n=2,280) used interview-based instruments to assess depression, and 11 studies (n=8,082) used self-report instruments. The OR for interview-based instruments was 3.69 (95% CI, 2.05–6.63; $P<.001$), and for self-report instruments, it was 1.83 (95% CI, 1.51–2.23; $P<.001$), which was significantly different ($\chi^2=2.22$, $P=.03$).

All studies reporting on cardiac mortality used self-rating instruments, so no subgroup analysis could be performed.

For the outcome cardiac events, 7 studies (n=1,260) used interview-based instruments to assess depression, and 11 studies (n=8,859) used self-report instruments. The OR for interview-based instruments was 1.96 (95% CI, 0.99–3.89; $P<.05$), and for self-report instruments, it was 1.53 (95% CI, 1.35–1.73; $P<.001$), which was not significantly different ($\chi^2=0.70$, $P=.48$).

There were no changes in the frequency of use of self-report instruments and interviews over time.

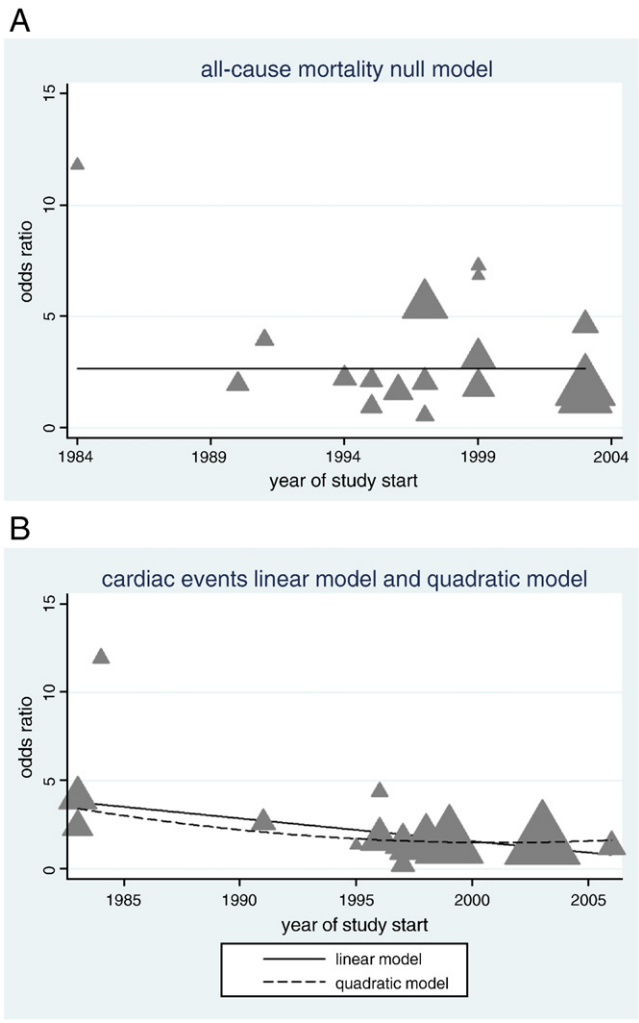

Fig. 4. (A) Association between the year of study start and OR for all-cause mortality. (B) Association between the year of study start and OR for cardiac events.

3.7. Differences between smaller studies and larger studies

Studies reporting on all-cause mortality were divided into two subgroups. The subgroup of nine studies with each less than 400 subjects contained 2,012 patients, and the subgroup of eight studies with each more than 400 subjects contained 8,350 patients. The OR for the smaller studies was 2.25 (95% CI, 1.38–3.66), and for the larger studies, it was 2.30 (95% CI, 1.65–3.20). There was no significant difference between the ORs (χ^2=0.07, P=.94).

For the outcome cardiac mortality, the studies were again divided into two subgroups. The subgroup of three studies with each less than 330 subjects contained 852 patients, and the subgroup of three studies with each more than 330 subjects contained 2,491 patients. The OR for the smaller studies was lower than that for the larger studies [1.90 (95% CI, 1.06–3.48; P=.03) vs. 3.92 (95% CI, 2.24–6.88] P<.001)], and this difference was not significant but showed a trend (χ^2=1.76, P=.08).

Finally, studies reporting on cardiac events were divided into two equal subgroups with nine studies. The subgroup of nine studies with each less than 400 subjects contained 1,700 patients, and the subgroup of nine studies with each more than 400 subjects contained 8,419 patients. The OR for the smaller studies was higher than that for the larger studies [1.74 (95% CI, 1.01–2.98; P=.04) vs. 1.53 (95% CI, 1.37–1.71; P<.001)]. The difference was not significant (χ^2=0.45, P=.65). Finally, for all three outcome types, there were no changes of study size over time.

3.8. Quality assessment

Studies were evaluated on six quality aspects. First, the preferred sample size was at least 25 patients in the depressed and in the nondepressed groups. In all studies, the number of nondepressed patients was over 25 (average n=400; range, 54–1823). The number of depressed patients was lower than 25 in three studies (average n=175; range, 4–920). Second, studies were assessed on representativeness of the population. The majority of studies (19) did not have any unusual inclusion or exclusion criteria. Exclusion criteria such as those based on the presence of dementia, the presence of other major psychiatric disorders and being unable to speak the researchers' language were not considered unusual. Third, it was assessed whether there was more than 25% loss to follow-up. Thirteen studies did not have any loss to follow-up. In the remaining studies, loss to follow-up was, on average, 5% (range, 0.2%–17%), and none reported loss to follow-up over 25%. Six studies did not report the number of patients lost to follow-up. Fourth, it was assessed whether studies adjusted for at least three of the following cardiac risk factors in their adjusted analyses: hypertension, smoking, hypercholesterolemia, diabetes mellitus, LVEF or previous MI. Twelve analyses were adjusted for at least three of these risk factors, 16 analyses were not adjusted for at least three of these factors and 4 analyses were not adjusted or did not report the variables they adjusted for. Fifth, it was assessed whether clinical end points were scored adequately, that is, by means of central death registry, chart review or independent blinded end-point committee. Three studies did not report how they scored the clinical end point, and three other studies did not use an adequate method (but patient or family self-reports only). Finally, it was assessed whether depression was measured using a structured diagnostic interview or a self-report instrument. The majority of the studies (17) used self-rating instruments, six studies used a standardized structured clinical interview and four studies used both. An overview of the quality assessment of the included articles is listed in Table 4.

The effects of the quality criteria on the association between post-MI depression and prognosis for sample size, type of depression measurement instrument and adjustment for confounders were assessed in the

Table 4
Quality assessment included studies

Author and article	Sample size	Representativeness of population	% lost to follow-up	Factors controlled for	Clinical end points scored adequately	Type of depression measurement instrument
Ahern et al. [1]	351 subjects	>75 years and women with child-bearing potential excluded	1	LVEF, previous MI, β-blockers, digitalis, anxiety, anger, social desirability, social support, mood states, type A–B	NA	Self-rating
Carney et al. [13]	1,328 subjects	No unusual inclusion or exclusion criteria	NA	ENRICHD all-cause mortality risk score; initial BDI score; SSRI use	Standardized, group-masked classification of major end points, death certificates	Interview
De Jonge et al. [14]	468 subjects	No unusual inclusion or exclusion criteria	0	Age, gender, education level, LVEF, revascularization	Patient interviews, hospital records, data from treating specialist, data from primary care physician	Interview
Denollet et al. [15]	416 subjects	age <30 years excluded	0	Age, gender, cardiac history, LVEF, invasive treatment, statins, aspirin, diuretics, SSRIs, BMI	Medical records	Self-rating
Doyle et al. [16]	433 subjects	No unusual inclusion or exclusion criteria	0	Age, sex	Primary care physicians for vital status, date of death from national births, marriages and deaths registry	Self-rating
Doyle et al. [17]	285 subjects	No unusual inclusion or exclusion criteria	5	Age, sex, smoking, diabetes, history of CHD, history of revascularization, length of hospital stay, LVEF	Medical records	Self-rating
Drago et al. [18]	98 subjects	No unusual inclusion or exclusion criteria	2	Age, gender, diabetes mellitus, dyslipidemia, previous AMI, anterior AMI, nonpreserved LVEF, acute treatment with thrombolysis or primary coronary angioplasty and HRV value	Medical examination, telephone interview or ambulatory examination, death certificates diagnosis for fatal events	Both
Frasure-Smith et al. [19]	896 subjects	No unusual inclusion or exclusion criteria	0	Age, smoking, LVEF, non-Q-wave MI, Killip class	Patient or family contacts, Quebec Medicare data, 2 independent raters	Self-rating
Frasure-Smith et al. [20]	222 subjects	No unusual inclusion or exclusion criteria	0	Anxiety, history of major depression, previous MI, LVEF, Killip class, ACE inhibitors at discharge	Contacting patients, family members, committee of cardiologists reviewed death certificates, ambulance and hospital records	Both
Irvine et al. [21]	301 subjects	No unusual inclusion or exclusion criteria	5	Previous MI, previous CHF, social participation, social network contacts, dyspnea/fatigue	Blinded external validation committee	Self-rating
Kaufmann et al. [22]	331 subjects	No unusual inclusion or exclusion criteria	0	Ejection fraction, previous MI, CHF, CABG, previous stroke, diabetes, age, hypertension, family history of CAD	Recontacting patients at home	Interview
Ladwig et al. [2]	553 subjects	Female patients and >66 years excluded	0	Recurrent MI, late potentials, dyspnea, occurrence of triplets or more complex arrhythmias in 24-Holter ECG	Home physician, hospital physician, relatives, bystanders	Self-rating
Lane et al. [23]	288 subjects	No unusual inclusion or exclusion criteria	6	Age, partner status, living alone, education, Peel index score, Killip class, length of hospital stay	Hospital patient information system	Self-rating
Lane et al. [24]	288 subjects	No unusual inclusion or exclusion criteria	1	Not stated	Hospital and general practician records, death certificates	Self-rating
Lauzon et al. [25]	550 subjects	No unusual inclusion or exclusion criteria	0	Age, sex, prior MI, history of previous angina, anterior location of infarct, diabetes mellitus, hypertension, smoking	Central death registry	Self-rating
Lesperance et al. [26]	222 subjects	No unusual inclusion or exclusion criteria	0	History of major depression, BDI >10, age >65 years	Contacting patients or family members	Interview
Mayou et al. [27]	344 subjects	No unusual inclusion or exclusion criteria	0	NA	Death certificates, autopsy records and Office of National Statistics data	Self-rating

Nakatani et al. [28]	1,803 subjects	No unusual inclusion or exclusion criteria	0	Age, sex, diabetes mellitus, hypertension, hyperlipidemia, smoking, history of M, Killip class > or = II, anterior infarction, reperfusion antiplatelet agents, ace inhibitors, β-blockers	Research outpatient clinic, verbal or written contact with patients or their family members	Self-rating
Parakh et al. [29]	284 subjects	No unusual inclusion or exclusion criteria	0	Age, diabetes, previous MI, Killip class, treatment of MI, LVEF, Q-wave MI, creatine kinase, renal insufficiency, lung disease, length of stay, aspirin use, physical function (SF-36)	Social Security Death Index	Both
Parashar et al. [30]	1,881 subjects	No unusual inclusion or exclusion criteria	11	Age, race, sex, medical history (diabetes, hypertension, COPD, smoking, prior MI), severity of MI (ST-segment elevation), LVEF	Contacts with family members, Social Security Death Master File, patient contacts	Self-rating
Rafanelli et al. [31]	61 subjects	No unusual inclusion or exclusion criteria	0	Age, sex, absolute CV risk (MI complications, LVEF, residual ischemia, ventricular arrhythmias, smoking, diabetes, hypertension, cholesterol, triglycerides, fibrinogen, leukocytes, intermittent claudication, heart rate	NA	Interview
Rumsfeld et al. [32]	634 subjects	Only patients with heart failure included	NA	Age, gender, race, BMI, systolic blood pressure, LVEF, prior heart failure and MI, atrial fibrillation, reperfusion or revascularization during hospitalization, smoking, hypertension, diabetes mellitus, dyslipidemia, COPD, stroke or TIA, renal failure, moderate to heavy alcohol use, ACE/ARB, β-blockers, diuretics, aspirin, statins	All-cause mortality and cardiovascular death or hospitalization adjudicated by a blinded critical events committee	Self-rating
Shiotani et al. [33]	1,042 subjects	No unusual inclusion or exclusion criteria	1	Age, diabetes mellitus, hypertension	Hospital records, telephone interviews with patients or family	Self-rating
Silverstone [3]	108 subjects	No unusual inclusion or exclusion criteria	NA	None	Not reported	Interview
Smolderen et al. [34]	2,347 subjects	No unusual inclusion or exclusion criteria	10–17	Age, sex, race, diabetes mellitus, prior coronary artery disease, stroke, chronic renal failure, chronic lung disease, chronic heart failure, nonskin cancer, current smoking, BMI, marital status, education, insurance status, working status, ST-elevation AMI, LVEF, heart rate, angiography, revascularization, percent and number of quality of care indicators received	Patient reports (telephone interview), Social Security Death Master File	Self-rating
Sørensen et al. [35]	761 subjects	>76 years excluded	NA	Age above 65 years, being single, non-Q-wave infarction, ejection fraction, 40% and high workload	National Register of Patients, National Register of Causes of Death	Self-rating
Steeds et al. [36]	131 subjects	No unusual inclusion or exclusion criteria	NA	Size of MI, rate of thrombolysis, in-hospital complications but not clear for: calcium antagonists, β-adrenoreceptor antagonist at discharge	UK National Health Service central register	Self-rating
Strik et al. [37]	318 subjects	Females and patients with previous MI excluded	0	Age, LVEF, antidepressants	Diagnosis by attending cardiologist	Interview
Sydeman, [38]	101 subjects	<35 years excluded	7	State anger, LVEF	Patient reports	Both
Thombs et al. [39]	416 subjects	No unusual inclusion or exclusion criteria	0.20	age, Killip class, history of AMI, gender, marital status, history of angina, diabetes, smoking	12-Month patient questionnaire, patient/family reports, GP's and specialist physicians	Self-rating
Welin et al. [40]	275 subjects	Patients with previous MI excluded	3	Sex, LVEF, dyspnea after infarction, ventricular dysrhythmia at 3 months, diabetes mellitus, social activities	Death certificate, physician diagnosis	Self-rating

BMI, body mass index; AMI, acute myocardial infarction; ACE, angiotensin-converting enzyme; CABG, Coronary Artery Bypass Grafting; CAD, Coronary Artery Disease; CHF, chronic heart failure; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; ENRICHD, Enhancing Recovery in Coronary Heart Disease; HRV, Heart Rate Variability; SF-36, Short Form-36; SSRI, Selective Serotonin Reuptake Inhibitor.

secondary analyses. These analyses revealed that sample size did not affect the strength of the association reported, that studies using structured diagnostic interviews had higher ORs for all-cause mortality than did studies using self-rating instruments and that the association between post-MI depression and prognosis was attenuated when adjusted for confounders. The other quality criteria were assessed in sensitivity analyses. These analyses revealed no differences in results with regard to specific inclusion or exclusion criteria, loss to follow-up or end-point scoring method.

4. Discussion

4.1. Association between post-MI depression and prognosis

Unadjusted ORs show that patients with a post-MI depression have a 2.25 times increased risk of all-cause mortality, a 2.71 times increased risk of cardiac mortality and a 1.59 times increased risk of new cardiac events. These ORs are similar to those found in earlier meta-analyses [6,7].

Individual adjusted associations were lower (on average, 21%) than unadjusted associations in all but one of the eight studies reporting associations adjusted for baseline demographic and medical variables. This attenuation was found in previous similar meta-analyses of the association between depression in cardiac patients and prognosis. A meta-analysis of MI patients, for example, found a reduction in association of 41% after adjustment for possible confounders [7] Others also found a reduction, though less pronounced [6,8]. One possible explanation may be reverse causality: depression does not cause cardiac events or death, but the severity of the cardiac disease causes both a poorer prognosis and more depressive symptoms [7]. The fact, however, that after adjustment for disease severity, depression is still associated with poorer prognosis suggests that it is an independent risk factor. Most likely, the association is bidirectional. In addition, other variables, such as smoking and age, may affect the association, not just as confounders, but also as mediators of the association. When there is reverse causality or confounding, the pooled ORs adjusted for disease severity and other confounders will probably turn out lower than unadjusted pooled ORs [43].

Unfortunately, we could not provide a pooled association that is consistently adjusted for the same variables across studies, as each study adjusts for a different set of variables. The only way to solve this problem is to perform a meta-analysis of individual patient data of the original studies and adjust for the same variables.

4.2. Changes in ORs over time

ORs were expected to decline over time, and such a decline was found for the outcome cardiac events, showing a small but significant decline of about 0.1 for each progressing year. This means that the apparent effect of depression on new cardiac events has become smaller. Too little is known so far about the mechanisms of this association to be able to explain this decline. For the outcomes all-cause mortality and cardiac mortality, there were no significant changes in ORs over time. No mentionable changes were found in the frequencies of mortality, cardiac events or depression that could help explain the fact that the association did decline for cardiac events, but not for mortality.

4.3. Subgroup analyses: depression measurement and sample size

The two subgroup analyses, based on the type of depression measurement instrument and number of subjects per study, revealed interesting results. The ORs for diagnostic interviews were significantly higher than those for self-rating instruments for all-cause mortality. This makes sense, as the fact that studies using (semi-)structured diagnostic interviews categorize patients with more severe depressive symptoms as depressed, whereas studies using self-rating instruments may include more patients, as they often include patients with mild and moderate depressive symptoms as well. Major depression is likely to have a stronger association with adverse outcomes than less severe depressive symptoms when there is a dose–response relationship. In addition, it has been suggested that standard cutoff scores for self-rating instruments lead to an overestimation of depression severity. More nondepressed patients may be rated as depressed than when structured diagnostic interviews are used. This can explain why the strength of the association between post-MI depression and prognosis is weaker for depression assessed with self-rating instruments than for structured interview-based instruments.

Contrasting results were found in other meta-analyses on depression in CHD patients. Nicholson et al. [7] found that studies using clinical measures of depression reported weaker associations between depression and prognosis than did studies using symptom assessments. Barth et al. [6] found no difference in the association between post-MI depression and prognosis as measured with (semi-)structured diagnostic interviews or self-report instruments and prognosis. In the current meta-analysis, smaller studies did not report significantly higher ORs than did larger studies, and sample size did not change over time. This indicates that publication bias did not affect the results.

5. Conclusion

This meta-analysis shows that depression has been consistently associated with a worse prognosis after MI over the past 25 years. The association between post-MI depression and impaired prognosis is stable over time for mortality, but shows a slight decline for new cardiac events. These results once again emphasize that depression in post-MI patients not only deserves attention as a debilitating

condition in itself but also remains a signal of an increased risk of cardiovascular events and mortality.

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Appendix 1: Search terms

PubMed

("mood disorders" [MeSH] OR depression [MeSH] OR depression [tiab] OR depressive [tiab]) AND ("myocardial infarction" [MeSH] OR "myocardial infarction" [tiab])

through January 5, 2011, humans only

Embase

("mood disorder" OR "depressive symptoms" OR "depressive symptomatology" OR depressed)

AND

("heart infarction" OR "myocardial infarction")

through January 5 2011, map to preferred terminology, explosion search, search terms must be major focus, search humans only, Embase only.

Psychinfo

((major depression) OR depression OR depressive)

AND

((myocardial infarctions) OR (myocardial infarction))

through January 5, 2011, humans only

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